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Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids

Available online 20 January 2025, 159595

In Press, Journal Pre-proof What's this?

Metabolomic and gene networks approaches reveal the role of mitochondrial membrane proteins in response of human melanoma cells to THz radiation

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Received 2 June 2024, Revised 14 January 2025, Accepted 15 January 2025, Available online 20 January 2025.

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Highlights

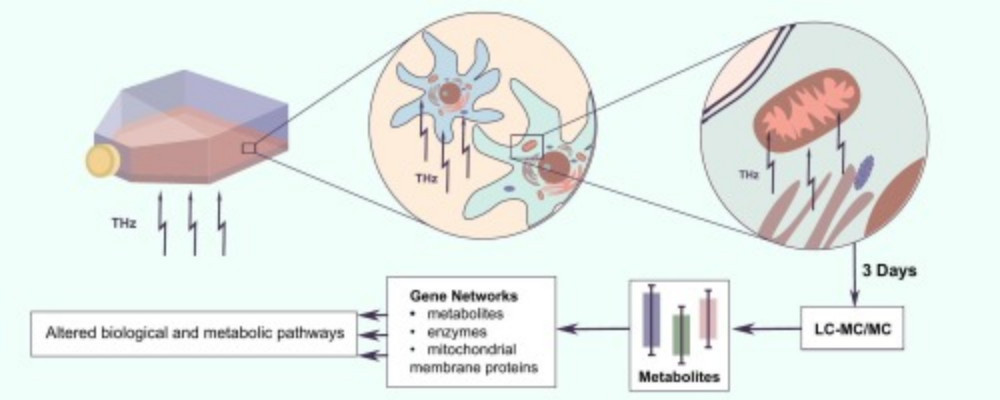
- THz radiation exposure induced significant changes in the levels of 40 metabolites, especially those related to purine and pyrimidine pathways. Lipids, such as ceramides and phosphatidylcholines, were also affected by this exposure.
- Gene network reconstruction identified mitochondrial membrane proteins, including components of the respiratory chain complex, ATP synthase, and lipid rafts, as key regulators of the enzymes involved in biosynthesis and degradation of the significantly altered metabolites.
- THz radiation induces reversible disruption of lipid raft macromolecular structure, altering mitochondrial molecule transport while maintaining protein integrity.
- Importantly, the metabolic effects observed were specific to THz radiation and were not due to heating, as evidenced by the distinct responses in control cells exposed to infrared radiation.

Abstract

Terahertz (THz) radiation has gained attention due to technological advancements, but its biological effects remain unclear. We investigated the impact of 2.3 THz radiation on SK-MEL-28 cells using metabolomic and gene network analysis. Forty metabolites, primarily related to purine, pyrimidine synthesis and breakdown pathways, were significantly altered post-irradiation. Lipids, such as ceramides and phosphatidylcholines, were also affected. Gene network reconstruction and analysis identified key regulators of the enzymes involved in biosynthesis and degradation of significantly altered metabolites. Mitochondrial

membrane components, such as the respiratory chain complex, the proton-transporting ATP synthase complex, and components of lipid rafts, reacted to THz radiation. We propose that THz radiation induces reversible disruption of the lipid raft macromolecular structure, thereby altering mitochondrial molecule transport while maintaining protein integrity, which explains the high cell survival rate. Our findings enhance the understanding of THz biological effects and emphasize the role of membrane components in the cellular response to THz radiation.

Graphical abstract



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Introduction

Terahertz radiation (THz, T-rays) is located between the microwave and infrared regions of the electromagnetic spectrum. The range of frequencies for T-rays is from 100 GHz to 10 THz Modern technologies based on the use of infrared radiation (IR) and terahertz electromagnetic waves are widely used in biomedical sciences and continue to develop rapidly [1]. At the same time, unlike the well-studied visible and ultraviolet regions of the spectrum, the infrared and terahertz regions of the electromagnetic spectrum are not fully studied [2].

This part of the spectrum range is relevant to many important physical, chemical, and biological processes. Due to THz absorption by the atmosphere, living systems in nature do not interact with terahertz radiation and have not evolved to develop protective mechanisms against it. Therefore, studying the effects of THz exposure on biological systems is crucial for safe development and application of this technology [3].

Scientific research and technological innovations in recent years have led to the development of new sources of THz radiation and its detectors, making it possible to utilize this part of the electromagnetic spectrum in various applications such as THz imaging [4], civil security systems [5], pharmaceuticals [6], data transfer for the next generation of 6G communication, and more [7]. Due to the growing interest in THz technology, the Tera-Hertz Radiation in Biological Research, Investigation of Diagnostic Potential Genotoxic Effects (THz-BRIDGE) project was initiated to study the potential effects of this radiation. Based on the project's findings, it was concluded that THz radiation was safe [8], however, in 2015, the Scientific Committee on Emerging and Novel Health Risks (SCENIHR) published a report on the potential health risks associated with electromagnetic radiation, with a focus on the effects of THz radiation on the skin and cornea [9]. In addition, frequencies above 100 GHz, from which the terahertz range begins, are promising for 6G communications [10]. The US Federal Communications Commission (FCC) recommends bands from 95 GHz to 3 THz for the development of a new 6G communication standard [11], which raises the question of deeper studies of these frequencies. At the moment, many empirical studies have been conducted at frequencies below 1 THz and a short exposure time, in which delayed effects have not been evaluated for more than a day.

NovoFEL is a unique facility for generating THz radiation in the range of 90–400 μm, which can be used to obtain a wavelength with a relative line width of 10–2. Numerous experiments were conducted on *E. coli* with different wavelengths and it was shown that the most pronounced effect was detected for a frequency of 2.3 THz [12].

Currently, there is data obtained by the laboratory of Dr. Sergei Peltek [[13], [14], [15], [16]] and others for proteomic analysis of prokaryotic *E. coli* and *G. icigianus*, and expression analysis of human embryonic stem cells (hESC) irradiated with THz at the NovoFEL (Budker Institute of Nuclear Physics, Novosibirsk, Russia), with a frequency of 2.3 THz [17]. Proteomic changes in *G. icigianus* were observed 15 min after irradiation; cell protection systems from oxidative stress were also activated, and changes in energy metabolism occurred. In *E. coli* K12 JM109, the expression of genes responsible for aggregation was affected, as well as of those controlling cell division and associated with oxidative stress. The effect of THz radiation on hESC caused a change in the expression of <1 % of genes associated with mitochondrial metabolism.

It is known from the physical characteristics of THz that its frequency correlates with rotational movements, weak hydrogen bonds and Van der Waals interaction forces [18,19]. Based on this, it is logical to assume the effect of THz on macromolecules. Since the

penetration of THz radiation into the human body is limited to the submillimeter range, its effect on the skin is one of the most relevant for potential clinical applications [4].

Melanoma is a malignant tumor that occurs most often in the skin, less often in the retina or mucous membranes [20]. Cheon et al. [21] proposed a method of demethylation of the DNA of SK-MEL-3 melanoma cells using THz radiation as a potential technique for therapeutic use. Zhou et al. [22] have shown that THz irradiation with an intensity of 500 mW/cm2 caused morphological changes in melanoma cells, but did not initiate their apoptosis. In this regard, it is necessary to assess the metabolism of melanoma cells after exposure to THz, as these data have not yet been reported in the literature.

Omics technologies for studying biological systems have led to a new understanding of biochemical processes. Their application has made it possible to study and analyze large amounts of data related to the structure and functioning of biological systems more efficiently [23]. One of the promising areas of omics technology is the use of the metabolomic approach. Metabolomics is a new and rapidly evolving concept in bioanalytical chemistry that aims to quantify small molecules (with a molecular weight <1.5 kDa) present in a biological system in any of its physiological states [24]. Traditionally, biological fluids and tissues have been analyzed in metabolomics, however, in recent years, the field of single cell and single cell line metabolomics has seen significant development [25,26]. Currently, there are no published studies on metabolomics in human eukaryotic cells after THz irradiation. We could find only one metabolomics study of leaves of a plant that was grown under THz radiation [27].

Metabolomic screening of cells and cell lines allows researchers to study molecular pathogenesis by determining levels of hundreds of their metabolites [28]. By annotating metabolic pathways, it is possible to retrospectively identify metabolites, proteins, and genes that are affected by an external factor [29]. The increasing use of THz technologies in various fields necessitates accurate experiments to assess radiation safety and thoroughly examine THz-induced mechanisms at the cellular and tissue levels. Existing data on the biological effects of THz are limited and scattered, and their interpretation and establishment of mechanisms for non-thermal effects remain unresolved challenges. The study of factors influencing the response of living systems to THz radiation requires numerous experiments using unique facilities. Applying the metabolomic approach to studies of the effects of THz radiation on the living system allows us to obtain new data under various experimental conditions.

A promising approach for interpreting metabolomics data is gene network reconstruction. Previously, we developed an information system called ANDSystem, which is designed to

reconstruct gene networks based on the analysis of scientific publications and factual databases [[30], [31], [32], [33]]. ANDSystem was applied to the analysis of metabolic data and allowed us to explore the regulatory role of non-structural proteins of SARS-CoV-2 in the disruption of metabolic processes in patients with COVID-19 [34]. The application of the ANDSystem to the analysis of data from metabolic screening of blood plasma in patients with postoperative delirium has made it possible to reconstruct the molecular genetic mechanisms underlying metabolic disorders of sphingolipids [35].

This paper presents a study on the biological effects of terahertz irradiation with a frequency of 2.3 THz and a power of 0.056 W/cm^2 on SK-MEL-28 cells, using targeted metabolomic screening by liquid chromatography and tandem mass spectrometry (LC-MS/MS) and gene network analysis. In addition, cells were irradiated by IR to identify specific effects of terahertz radiation on the metabolomic profile that are not related to heating. In turn, the analysis of the cellular metabolomic profile allowed us to identify specific metabolites and metabolic pathways that are associated with THz radiation. In the current study, we set a goal to interpret changes in the metabolomic profile of cells irradiated with THz using a gene network approach. The reconstruction and analysis of gene networks were performed within the framework of the hypothesis about the role of mitochondrial membrane proteins in changes in the cellular metabolomic profile in response to THz radiation.

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Section snippets

Human melanoma cell line SK-MEL-28

The human melanoma cell line SK-MEL-28 (ATCC HTB-72), obtained from the collection of the Center for Genetic Resources at the Laboratory Animal Center of the Institute of Cytology and Genetics SB RAS (Novosibirsk, Russia), was used in this experiment. The cells were grown in a medium DMEM/F12 (1:1) with 15 mM HEPES (Biolot, Russia), supplemented with 10% fetal bovine serum (Capricorn, Germany) and 50 μg/mL gentamicin (Dalkhimpharm, Russia). The temperature was maintained at 37 °C in the …

Assessment of cell viability, MTT and clonogenic formation assays

Our experiments were conducted using the SK-MEL-28 cell line because of the possibility of rapid cultivation of a large amount of these cells. In addition, human skin is the main target for THz radiation in the development and implementation of new facilities that emit in this range of the electromagnetic spectrum. The first tests used in our study were aimed at assessing cell viability after irradiation. To establish the primary effects of THz radiation on cells, cell viability was assessed …

Discussion

The low penetrating power of THz radiation limits its effect to cell membranes, which explains the emphasis on membrane effects [54]. So, in the course of pilot experiments, we optimized the method of irradiating cells in culture flasks. It was found that the flasks have a low THz absorption coefficient, which means they have high permeability. However, these parameters can vary significantly between similar models from different manufacturers. The review [55] noted the importance of selecting …

Conclusion

For the first time, we systematically studied the biological effects and mechanisms of THz radiation on human melanoma cells (SK-MEL-28). Our findings show that THz radiation significantly affects metabolic processes, with changes depending on the duration of irradiation. The most pronounced alterations occurred in the degradation pathways of purines and pyrimidines, indicating disruptions in energy metabolism and nucleotide synthesis.

Key mitochondrial membrane proteins and enzymes were linked …

CRediT authorship contribution statement

Ekaterina A. Butikova: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nikita V. Basov:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Artem D. Rogachev:** Writing – original draft, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Evgeniy V. Gaisler:** Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, …

Funding

The experimental part of the study was carried out with the support of the Russian Science Foundation (Project No. 19-72-202) at the unique Novosibirsk Free Electron Laser installation using equipment from the Siberian Center for Synchrotron and Terahertz Radiation. The funds from the state project No. BC 2020-0039-1 have been used to conduct cell research. LC-MS/MS analysis has been conducted with the support of a state project No. FSUS-2020-0035. The authors also thank the state project No. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgments

The authors would like to acknowledge the Center for Genetic Resources of Laboratory Animals at the Institute of Cytology and Genetics SB RAS for the cell lines and equipment necessary for conducting cellular assays. The authors are grateful to the group of Budker Institute of Nuclear Physics SB RAS for providing terahertz generation. Also, the authors are thankful to Dr. Maria A. Aleshkova, MD, and Olga A. Zhupikova, MSc, for visualizing the manuscript. …

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